Stem cell models to analyze the role of mutated C9ORF72 in neurodegeneration

Grant Award Details

Stem cell models to analyze the role of mutated C9ORF72 in neurodegeneration

Grant Type: Basic Biology IV

Grant Number: RB4-06045

Project Objective: The goal of this project is to develop disease-in-a-dish models of C9ORF72 defects, a locus that has recently been tied to ALS and FTD, but for which almost nothing is known. The models will be used to test key hypotheses of pathogenesis and explore potential interventions.

Investigator:

Name:	Eugene Yeo
Institution:	University of California, San Diego
Type:	PI

Disease Focus: Amyotrophic Lateral Sclerosis, Neurological Disorders, Dementia, Neurological Disorders

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,260,360

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Stem cell models to analyze the role of mutated C9ORF72 in neurodegeneration

Public Abstract: Amyotrophic lateral sclerosis (ALS) is an idiopathic adult-onset degenerative disease characterized by progressive weakness from loss of upper and lower motor neurons. Onset is insidious, progression is essentially linear, and death occurs within 3-5 years in 90% of patients. In the US, 5,000 deaths occur per year and in the world, 100,000. In October, 2011, the causative gene defect in a long sought after locus on chromosome 9 for ALS, frontotemporal dementia (FTD) and overlap ALS-FTD was identified to be a expansion of a hexanucleotide repeat in the uncharacterized C9ORF72 gene. The goal of the proposed research is to generate human stem cell models from cells derived from ALS patients with the C9ORF72 expanded repeats and relevant control cells using genome-editing technology. We will also generate a stem cell model expressing the repeat independent of the C9ORF72 gene to study if the repeat alone is causing neural defects. Using advanced genome technologies, biochemical and cellular approaches, we will study the molecular pathways affected in motor neurons derived from these stem cell models. Finally, we will use innovative technologies to rescue the abnormal phenotypes that arise from the expanded repeat in human motor neurons. Completion of the proposed research is expected to transform our understanding of the regulatory and pathogenetic mechanisms underlying ALS and FTD, and establish therapeutic options for these debilitating diseases.

Statement of Benefit to California: Our research provides the foundation for decoding the mechanisms that underlie the single most frequent genetic mutation found to contribute to both ALS and FTD, debilitating neurological diseases that impact many Californians. In California, the expected prevalence of ALS (the number of total existing cases) is 2,200 to 3,000 cases at any one time, and the incidence is 750-1,100 new cases each year. The number of FTD cases is five times as many. Our research has and will continue to serve as a basis for understanding deviations from normal and disease patient neuronal cells, enabling us to make inroards to understanding neurological disease modeling using neurons differentiated from reprogammed patient-specific lines. Such disease modeling will have great potential for California health care patients, pharmaceutical and biotechnology industries in terms of improved human models for drug discovery and toxicology testing. Our improved knowledge base will support our efforts as well as other Californian researchers to study stem cell models of neurological disease and design new diagnostics and treatments, thereby maintaining California's position as a leader in clinical research.

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